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ISTA Pharmaceuticals

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August 4, 2003

Wiley Chambers, M.D.
Deputy Division Director
Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug Products
(HFD-550)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

Re: NDA 21-640, New 505(b)(2) NDA for Vitrase®
(ovine hyaluronidase)

Dear Dr. Chambers,

In accordance with 505(b)(2) of the Food, Drug and Cosmetic Act and 21 CFR 314.50, ISTA Pharmaceuticals, Inc. submits this 505(b)(2) New Drug Application (NDA) for Vitrase (ovine hyaluronidase). The proposed indication for Vitrase is as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. At this time we would like to confirm the acceptability to the Agency of the trade name Vitrase® for the proposed indication.

Hyaluronidase (previously marketed as Wydase) is considered by the FDA to be a medically necessary drug product and is currently on FDA's list of drug shortages because it is no longer manufactured by Wyeth Laboratories. The Vitrase formulation differs from the Wydase formulation only in that it is of ovine origin and is preservative-free. This proposed formulation would provide a safe, consistent and reliable supply of this product as an alternative to the existing supply, which is provided by compounding of bovine hyaluronidase by individual pharmacies.

Wydase was previously approved for and marketed by Wyeth Laboratories. ISTA's 505(b)(2) application relies on the Agency's previous findings of safety and efficacy for Wydase, as described in the Drug Efficacy Study Implementation (DESI) finding published in the Federal Register on September 23, 1970 (vol. 35, no. 185, pages 14800-14801). All patents and periods of exclusivity for the original product (Wyeth Laboratories NDA 6-343 for Wydase) in the United States have expired.

For nonclinical pharmacology and toxicology information and for clinical data, this 505(b)(2) application cross-references Wydase NDA 6-343 to which ISTA has not obtained a right of reference. For chemistry, manufacturing, and controls data and supportive nonclinical and clinical safety data, this NDA cross-references ISTA's NDA 21-414 and all amendments thereto for Vitrase, which is for the same formulation of ovine hyaluronidase administered by a different route (ophthalmic intravitreal injection) and for a different indication, i.e., for the treatment of vitreous hemorrhage to improve visual acuity and to facilitate the physician's ability to diagnose the underlying retinal pathology.

For this application:

- The NDA review and archival copies are submitted in paper format.
- Thirteen desk copies will be sent directly to Lori Gorski, Project Manager.
- The complete Archival copy (1 volume) is provided in a blue binder.
- The Chemistry, Manufacturing and Controls section (1 volume) is provided in a red binder and includes a cross-reference to NDA 21-414, which was submitted on September 30, 2002. Sterilization information, analytical methods and methods validation information are also included in this section.
- The Nonclinical Pharmacology and Toxicology section (1 volume) is provided in a yellow binder and includes a cross-reference to the corresponding section of NDA 21-414, which was submitted on January 3, 2002 and October 2, 2002.
- The Human Pharmacokinetics and Bioavailability section (1 volume) is provided in an orange binder and includes a cross-reference to Section 20.1 that requests a waiver of the requirement for evidence of in vivo bioequivalence due to the lack of supply of Wydase for comparison.
- The Microbiology section (CMC-related, 1 volume) is provided in a white binder and includes a cross-reference to the corresponding section of NDA 21-414, which was submitted on October 7, 2002.
- The Clinical section (1 volume) is provided in a tan binder and includes a cross-reference to the corresponding section of NDA 21-414, which was submitted on October 7, 2002.
- The Statistical section (1 volume) is provided in a green binder and includes a cross-reference to the corresponding section of NDA 21-414, which was submitted on October 7, 2002.
- The Field Submission Chemistry section (1 volume) will be provided on request in a maroon binder. Reference is made to NDA 21-414 whereby three (3) Field copies (volumes 2.1-2.26) were submitted to FDA offices in Denver and Los Angeles on October 9, 2002 and to Mr. Daniel Grabicki (International Inspections Staff) on January 15, 2003.
- All facilities that had responsibilities in the manufacture, testing or release of Vitrase, and those clinical sites that were selected by the Agency for inspection, have satisfactorily resolved all deficiencies that were identified at the time of the pre-approval inspections for NDA 21-414.

The user fee check to the FDA for this application was sent to the Mellon Client Service Center on July 29, 2003 under the User Fee Identification Number 4580. A User Fee Waiver Request was also submitted on July 29, 2003. The basis for this user fee waiver is the unmet medical need, i.e., lack of supply of Wydase and the interests of the public health.

The contact person for all correspondence concerning this NDA is:

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We look forward to your expedited review of this 505(b)(2) NDA. If you have any questions or comments, please do not hesitate to contact me.

Sincerely,
ISTA Pharmaceuticals, Inc.

Marvin J. Garrett

Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance

CC: Ms. Lori Gorski, Project Manager

2.2 Comparison of Draft Vitrase and Approved Wydase Labeling

Vitrase® (ovine hyaluronidase)	**Wydase® (hyaluronidase)**
DESCRIPTION Vitrase is a preparation of highly purified ovine testicular hyaluronidase, a protein enzyme. The exact chemical structure of this enzyme is unknown. Ovine hyaluronidase, dehydrated in the frozen state under high vacuum with the inactive ingredients listed below, is supplied as a sterile, nonpreserved, white, odorless, amorphous solid. The product is to be reconstituted with 0.9% Sodium Chloride Injection, USP, before use (see "Dosage and Administration"). Each vial of 7,440 U of ovine hyaluronidase contains 5 mg lactose, 1.92 mg potassium phosphate dibasic, and 1.22 mg potassium phosphate monobasic.	**DESCRIPTION** Wydase, a protein enzyme, is a preparation of highly purified bovine testicular hyaluronidase. The exact chemical structure of this enzyme is unknown. Wydase is available in two dosage forms: **Wydase Lyophilized** Hyaluronidase, dehydrated in the frozen state under high vacuum, with lactose and thimerosal (mercury derivative), is supplied as a sterile, white, odorless, amorphous solid and is to be reconstituted with Sodium Chloride Injection, USP, before use, usually in the proportion of one mL per 150 USP units of hyaluronidase (Wydase Lyophilized). Each vial of 1,500 USP units contains 1.0 mg thimerosal (mercury derivative), added as a preservative, and 13.3 mg lactose. Each vial of 150 USP units contains 0.075 mg thimerosal (mercury derivative), added as a preservative, and 2.66 mg lactose. **Wydase Stabilized Solution** A hyaluronidase injection solution ready for use, colorless and odorless, containing 150 USP units of hyaluronidase per mL with 8.5 mg sodium chloride, 1 mg edetate disodium, 0.4 mg calcium chloride, monobasic sodium phosphate buffer, and not more than 0.1 mg thimerosal (mercury derivative). The USP and the NF hyaluronidase units are the equivalent to the turbidity-reducing (TR) unit and to the International Unit.